

SPECTRUM OF RESPIRATORY INFECTIONS IN POST RENAL TRANSPLANT PATIENTS

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CERTIFICATE

This is to certify that the dissertation on “**SPECTRUM OF RESPIRATORY INFECTIONS IN POST RENAL TRANSPLANT PATIENTS**” is a record of research work done by **Dr.A.Sundararajaperumal** in partial fulfillment for M.D.BRANCH- XVII (T.B. AND RESPIRATORY DISEASES) EXAMINATION of The Tamilnadu Dr. M.G.R.Medical University to be held in March 2010. The period of study is from October 2007 to October 2009.

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INTRODUCTION

In the last few decades, kidney transplantation has evolved into a practical therapeutic modality for the management of chronic renal failure¹; but along with the realized dream of a successful renal allograft come the harsh reality of a plethora of opportunistic infections due to the necessity of immunosuppression.

Infections remain the most important cause of morbidity and mortality among renal transplant recipients. In tropical countries like India, there are numerous factors like hot and humid climate, lack of hygiene practices, poor socioeconomic status, and the endemic nature of certain infections contribute to their high incidence², besides immunosuppression, which is the major factor.

The lung has special vulnerability to infection. Respiratory tract infections have been implicated as the single largest cause of infection related mortality in renal transplant recipients³. Appropriate treatment at the right time of post transplant respiratory infections could save these patients. This requires the knowledge about the spectrum of microorganisms causing these infections and the time of development of such respiratory tract infections. Aggressive diagnostic approaches including various tests are required to make an early diagnosis and to start appropriate treatment.

The present study was undertaken to know about the etiological factors for respiratory infections in post renal transplant patients, their common clinical presentation, and the role of bronchoalveolar lavage in its diagnosis.

AIM OF THE STUDY

1. To study the spectrum of bacterial, mycobacterial and fungal infections of lower respiratory tract and their sensitivity pattern in post renal transplant patients.
2. To document the common mode of clinical presentation for respiratory tract infection in post renal transplant patients.

REVIEW OF LITERATURE

Microbial spectrum

A host of microbes, ranging from common viral and bacterial pathogens to exotic fungal and protozoal agents, has been reported to cause pulmonary infections in the immunocompromised host.

World wide status

Bacteria: During the early years of transplantation, aerobic gram negative bacilli (*Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) and *Staphylococcus aureus* were frequent causes of pneumonia in renal allograft recipients⁴. These pathogens are commonly hospital acquired and are responsible for a high mortality rate. In some transplant centers, these bacteria and *Streptococcus pneumoniae* still remain the most important causes of pneumonia⁵. As the pathological diagnosis is difficult to establish by sputum analysis alone, management depends on recovery of the causative organisms from blood culture, trans-tracheal aspirate and/or a bronchoscopy specimen utilizing a sheathed brush.

Mycobacterium tuberculosis- Renal transplant patients have an increased risk of pulmonary infection due to *Mycobacterium tuberculosis* and atypical mycobacteria⁶. Because of the compromised host defense status of these patients, disseminated infection is common. Unusual pulmonary presentations may be seen in transplant patients with

tuberculosis and to further complicate matters, a prior history of tuberculosis exposure or a positive tuberculin test may not be obtained. Thus, the index of suspicion of mycobacterial infection must always remain high in renal transplant patients with pulmonary infiltrates. If expectorated sputum is negative by acid fast stain, fiberoptic bronchoscopy should be considered to obtain adequate specimens for repeat staining as well as mycobacterial culture.

Fungi: During the early years of transplantation, fungi were recognized as a common and highly lethal group of pathogens in transplant recipients. Although the incidence of fungal pneumonia has declined significantly, this disease remains one of the most serious infections in renal transplant recipients⁷. The four major fungal etiologies of pneumonia to be considered in renal allograft recipients are *Aspergillus* species, *Histoplasma capsulatum*, *Coccidioides immitis* and *Cryptococcus neoformans*; several epidemiologic and clinical features can be helpful in distinguishing among these. Aspergillosis is usually acquired in the hospital and often closely follows cytomegalovirus disease while Coccidioidomycosis and histoplasmosis are generally restricted to areas of endemic infection. Although disseminated disease is common to all pulmonary mycoses, cryptococcosis and histoplasmosis frequently present without obvious pulmonary involvement.

Pneumocystis carinii- *P. carinii* pneumonia may accompany other infections in patients treated with immunosuppressants but can itself cause respiratory insufficiency and death⁸. The classic pattern is readily recognized and can usually be diagnosed on the basis of the patient's history, physical examination and chest radiography. These patients usually have severe shortness of breath, low grade fever and a dry, non-productive cough. The degree of dyspnea far exceeds the other toxic signs and there may be cyanosis in the absence of any sputum or fever. There is a diffuse bilateral alveolar infiltrate extending from the hilum to the very periphery of the lung. This pneumonia consists of thick proteinaceous intra-alveolar exudates composed primarily of the organisms themselves. If recognized early, this condition can be treated and cured, since it may run an indolent course. The GMS stain (Gomori methenamine silver stain) was used for confirmation, and BAL is the method of choice for diagnosis.

Munda et al (1976) recorded forty six episodes of pulmonary infection in 41 patients during a seven year study period in which 187 renal transplants were performed⁹. Five patients had two episodes of pulmonary infection each. Twenty four patients recovered and seventeen died (41.5%). The etiologic agents diagnosed were primarily bacterial (74%), with protozoa, fungi and viruses appearing less frequently. In 35 episodes, a single etiologic agent was found but 11 were caused by two or more agents.

In a study by Huertas et al (1976), pneumonia developed in 33 of the 266 renal transplant recipients while they were on immunosuppressive therapy¹⁰. The majority of cases was bacterial in origin and developed during the first two postoperative weeks. Cases of fungal pneumonia were fewer and developed later. The mortality was 51.5% for all cases of pneumonia. The organisms identified were *K. pneumoniae* (30%), Enterobacteriaceae (30%), *S. fecalis* (24%), *H. influenzae* (24%), *P. aeruginosa* (21%), *E. coli* (18%), *A. fumigatus* (15%), *H. parainfluenzae* (12%), *P. mirabilis* (9%), *P. carinii* (9%), *S. aureus* (9%), *P. morgagnii* (6%), CMV (6%), Herellea (6%), *C. albicans* (3%), Serratia (3%).

Stake et al (1976) analysed pulmonary complications in 77 renal transplant patients¹¹. They found complications to be significantly higher in men. The mortality rate due to these chest infections was 14%. They found the causative organisms to be bacteria, *Pneumocystis carinii*, CMV and fungi.

Webb et al, in 1978, studied 68 episodes of pulmonary complications in 52 of 416 renal transplant patients treated with low dose immunosuppression¹². They found 44 infectious complications with 75% of these being wholly bacterial. Eight (18%) patients died of chest infections of which 7 had bacterial pneumonia but other infections were also present in 5.

Marshall et al¹³ (1980), in a retrospective review of 101 renal transplant cases, identified 14 cases of Legionnaires' disease. In 1984, Gombert et al¹⁴ also described five cases of nosocomial legionellosis in renal transplant recipients. Legionellosis was confirmed by seroconversion or direct fluorescent antibody.

Heurlin et al (1989) carried out a two year study of pneumonia in renal transplant recipients¹⁵. The microbiologic etiology of pneumonia in 34 renal transplant patients with clinical and x ray evidence of pulmonary parenchymal disease was studied. CMV was found to be the most common etiology (18 cases), bacterial pneumonia was seen in 11 patients, *Pneumocystis carinii* in 4 patients and *Candida albicans* in one patient. The overall mortality was 32%.

Hall et al¹⁶ (1994) retrospectively reviewed case records of renal transplant recipients from 1980 to 1992 to determine the prevalence and presentation of mycobacterial infection. They found 22 cases of mycobacterial infection in 487 patients with 21 cases being confirmed as *M. tuberculosis* and 1 unidentified Mycobacterium other than tuberculosis.

Kalender et al¹⁷ (2000) retrospectively evaluated opportunistic pulmonary infection in 274 kidney graft recipients from 1986 to 1998. They found the causes to be: pulmonary tuberculosis in 17 (42.5%) cases, aspergillosis in 8 (20%), CMV in 5 (12.5%), nocardiosis in 3 (7.5%), mucormycosis in 1 (2.5%) and unknown in 6 (15%).

The results of other studies from western countries are given in the following table .

Table No.1 Spectrum of pulmonary infection in studies from western countries (%)³¹

	Munda	Webb	Willcox	Sternbeg	Edelstein
	1978	1978	1990	1993	1995
Episodes	46	44	48	58	32
Bacteria	69.5	68.8	37.5	25.8	71.9
Nocardia	2.1	13.6	6.2	1.7	0
M. tub	4.3	2.2	22.9	0	28.1
P. carinii	13.0	6.8	8.3	10.3	0
Fungi	13.0	13.6	6.2	3.4	0
CMV	15.2	9.1	4.1	22.4	0
Others	2.1	0	6.2	3.4	0

Indian scenario

In the West, serious infections were noted in about 70% of the patients undergoing transplantation, with a near 40% fatal outcome¹⁸. Advances in diagnosis, prevention and therapy have reduced the mortality to less than 5% in developed countries^{19, 20}. In contrast, the lack of transplant registries has resulted in a dearth of information on the etiology and course of post transplant infections in tropical countries²like India Most of the available data are based on the experience of individual physicians from a limited number of centers. It is estimated that infections complicate the course of 50-70% of transplant recipients in tropical countries, with mortality ranging from 20-60%²¹. The

factors contributing to this dismal outcome include unhygienic conditions, hot and humid climate, late presentation, a lack of knowledge about the spectrum of organisms in these areas and high cost of life saving antimicrobial agents². The pattern of infections among transplant recipients in a tropical environment like ours differs from that seen in regions with temperate climate.

Bacterial infections: Among renal transplant recipients, bacterial infections originate most commonly from the lungs and the urinary tract ²². The causative organisms are the same as those prevalent in the general population. The etiologic agent often remains unidentified because of unavailability of isolation techniques and physicians tend to start broad spectrum antibiotics on empirical grounds. Pulmonary nocardial infections have been documented with a lower frequency among renal transplant recipients in the tropical regions. Similarly, legionella, an important cause of post transplant pneumonia in the temperate climate, has not been reported². In part, this discrepancy could be accentuated by the lack of awareness and unavailability of specific diagnostic techniques in the regions.

Mycobacterium tuberculosis: Because of its endemicity and the protean ways in which this disease can present, tuberculosis remains a frequent infection among renal transplant patients². Compared to the incidence of less than 1% in the United States and Europe and 4% in the Middle East, this infection is encountered in 10-13% of all renal transplant recipients in the tropical regions²³. Jha et al observed tuberculosis in 11.8% of

patients². The commonest presentation among transplant recipients in the tropics is with pleuropulmonary disease. About 20-40% patients present with fever of undetermined aetiology²⁴. The diagnosis is often made retrospectively after observing a complete response to antitubercular therapy. Although *M. tuberculosis* is the most common species isolated from these patients, infection with atypical Mycobacteria such as *M. kansasii*, *M. marinum*, *M. avium-intracellulare* and *M. fortuitum* has also been documented²³. Since these organisms are much less sensitive than *M. tuberculosis* to the conventional antitubercular agents, the species identification by culturing the specimen on appropriate media assumes considerable importance. Tuberculosis presents numerous diagnostic difficulties in renal transplant recipients. The classic picture of apical involvement on chest X ray is seen in only a minority of the allograft recipients, and now bronchoalveolar lavage has been shown to be useful in making an early accurate diagnosis of tuberculosis in this group of patients.

Fungal infections: Candida infection involves the lungs, usually as a secondary invader in those with a pre-existing infective or non-infective pulmonary lesion². The diagnosis is made by demonstrating the organism on BAL using a sheathed catheter. Sputum culture is not diagnostic because of the possibility of contamination with pharyngeal secretions where this organism usually resides. Pulmonary aspergillosis has been reported in a significant proportion of renal transplant recipients in tropical countries²⁵. Patients present with necrotising bronchopneumonia or, less commonly, with involvement of nasal sinuses. Zygomycosis can take the form of fulminant rhinocerebral

disease or necrotising pneumonia with massive haemoptysis²⁶.

Pneumocystis carinii: Before the introduction of cotrimoxazole prophylaxis, about 5-10% renal transplant recipients were observed to develop pneumonia due to *P. carinii*^{18, 27}. The frequency is higher in those on cyclosporine and the period of greatest risk is between 1 and 6 months after transplantation. Occasional clustering of cases has been reported in the tropical regions²⁸. Interstitial pneumonia leading to respiratory failure is a cardinal feature and the mortality approaches 60-100% in those with this complication.

Agarwal et al (1992) studied the spectrum of tuberculosis in renal transplant recipients in northern India²⁹. Of the 200 patients of end stage renal disease subjected to renal transplantation, 8 had pulmonary tuberculosis in the pre-transplant period. 11 patients developed tuberculosis for the first time during post transplant period. Only one case had reactivation of tuberculosis.

Sakhuja et al (1996) reported on the high incidence of tuberculosis among renal transplant recipients in India²⁴. They found 36 cases of tuberculosis in 305 renal transplant recipients over a period of 8 years. The infection was limited to the thoracic cavity in 41.7% cases and disseminated in 27.8% cases. Only one site (11.1%) was extrapulmonary. Most of the cases were encountered in the first post transplant year.

Jha R et al (1999) carried out a retrospective study analyzing pulmonary

infections after kidney transplant³⁰. Out of 142 consecutive renal transplant recipients who underwent live donor transplantation from June 1990 to May 1998, 27 had pulmonary infections. The aetiologic agents according to this study were Gram negative bacteria (2), Gram positive bacteria (2), nocardia (2), tuberculosis (10), aspergillosis (2), mixed bacterial and fungal infection (4), *Pneumocystis carinii* (2) and unconfirmed organisms (4).

In a study by Jha V et al (1999), carried out at the Postgraduate Institute of Medical Education and Research, Chandigarh, 39 episodes of infection were recorded in 34 patients over a period 1.5 years. M. tuberculosis was isolated during 10 episodes, pyogenic bacteria and *Pneumocystis carinii* in 6 each, candida in 4, aspergillus in 3, CMV in 3 and nocardia and mucor in 1 each³⁴. More than one organism was isolated during 5 episodes. They concluded that tuberculosis and *P. carinii* pneumonia were the most common non pyogenic infections in the first year after transplantation in developing countries.

In a study conducted at All India Institute of Medical Sciences, New Delhi, By Vikram kalra et al. (2002)³¹, 40 renal transplant recipients reported with 44 episodes of pulmonary infection during the study period. Out of the 44 episodes of pulmonary infection evaluated, single causative organism could be found in only 24 (54.5%) episodes and multiple etiologies were found in 15 (34.1%) episodes. No definitive cause could be found in 5 episodes. Out of 57 organisms isolated in the 44 episodes, 20 (45.4

%) were bacteria, 16 (36.3 %) each were M. tuberculosis and fungus, 3 were CMV infection and 2 were nocardia.

Spectrum of pulmonary infection in Indian studies are given in the following table.

Table No.2 Spectrum of pulmonary infections in Indian studies (%)³¹

	Modi '98 AIIMS	Jha R '99 Hyderabad	Jha V '99 PGI	Menon'02 K.E.M.	Vikram Kalra'03 AIIMS
Episodes	18	27	39	16	44
Bacteria	27.7	25.9	33.3	25	45.4
Nocardia	5.5	7.4	2.5	-	4.5
M. tub	50.0	37.0	30.7	-	36.3
P. carinii	-	7.4	15.3	6.2	27.2
Fungi	11.1	22.2	17.9	-	9.0
CMV	5.5	7.4	-	12.5	6.8

While focusing on infectious etiologies, in many instances, empiric, and broad spectrum antimicrobial therapies require to be instituted while a full evaluation is in progress, but these broad spectrum regimens cannot encompass all possible causative agents without producing unnecessary toxicity and expense. Failure to treat the causative process promptly can be devastating, particularly if the process is an infection in a severely immunodeficient patient like an allograft recipient³². Thus, it is important to establish the specific causative processes of a patient's pulmonary disease so that specific therapy can be instituted in a manner that promotes optimal efficacy and minimises toxicity and expense.

Various methods have been used as the diagnostic procedures to identify the microorganisms. These include sputum analysis, serology, blood culture, gastric aspiration³³ (for the analysis of tuberculosis), radiology (x ray, high resolution computerized tomography), fiberoptic bronchoscopy (BAL, mucosal brushing), transtracheal aspiration. Each method has its own advantages and shortcomings. Of these methods, fiberoptic bronchoscopy (FOB) is one of the most routinely used and accurate diagnostic aid.

MATERIALS AND METHODS

Study design : Prospective Cohort Study

Subjects and settings : Renal transplant patients being followed
up at the Department of Nephrology,

Department of Thoracic Medicine

Madras

Medical College,

Government

General

Hospital.

Duration of study : October 2007 - October 2009

Inclusion criteria

Transplant recipients attending the renal transplant clinic were included if they developed clinical and radiological (X ray chest or chest CT) features suggestive of pulmonary infection,

Exclusion criteria

1) Patients who have received antibiotics for more than **48 hrs.**

2) Patients who are too seriously ill to undergo BAL procedure with

i) Unstable myocardium

ii) Uncorrectable hypoxemia/hypercapnia

iii) Uncorrectable bleeding tendency

Study procedure

The study was conducted after obtaining approval from the Institutional Ethical Committee of Madras Medical College; Government General Hospital, Chennai. Patients seeking medical treatment at Department of Nephrology and Department of Thoracic medicine wards with manifestations of respiratory infections were explained about the study purpose and procedure. After getting written informed consent and taking inclusion and exclusion criteria into consideration, patients were included in the study. The selected patients were admitted in nephrology ward of Government General Hospital, Chennai. .

All patients underwent a comprehensive clinical assessment, which included a detailed history and a thorough physical examination. The patients were evaluated in detail for the history of present illness symptoms like fever, cough, haemoptysis, dyspnea, chest pain, history of previous chest infection (pre and post transplant), details of immunosuppression, past history of acute rejection and its therapy, recent IV antibiotics. History of other risk factors like diabetes (pre and post transplant) and serological virology status hepatitis B and C, and CMV. (Appendix I)

Clinical examination

A detailed clinical examination was carried out. Each patient was assessed for anemia, cyanosis, lymph nodes, scars and sinuses and icterus. Special emphasis was

given to the respiratory system for respiratory rate, findings related to pneumonia or pleural effusion and evidence of respiratory distress.

Investigations

The investigations included general laboratory tests, radiological assessment of the pulmonary lesion as well specific investigations to isolate the causative organisms.

a) Laboratory tests

This included Blood haemoglobin, complete blood counts, ESR. serum biochemistry included blood sugar, renal function test (blood urea, serum creatinine), liver function test (serum bilirubin, SGOT, SGPT, total proteins, albumin, globulin)

b) Sputum

Sputum specimen was received from the patient on first day of admission submitted for direct smear examination by Gram's stain, staining for demonstration of fungal elements using KOH mount. Three specimen of sputum, one on first day of admission and two on second day of admission including a early morning sample was collected and submitted for Ziehl-Nielson stain (Z-N) for acid fast bacilli (AFB)

c) Fiberoptic bronchoscopy and bronchoalveolar lavage

On second day of admission, patients undergoing bronchoscopy were explained

the nature of the procedure, its possible benefits and risks, in detail. Another written informed consent was obtained and the patient was kept fasting at least 4 hours prior to the procedure. Inj. Glycopyrrolate 0.2mg i.m was given as premedication. The fiberoptic bronchoscope was introduced intranasally after topical anaesthesia lignocaine. After routine examination of the tracheobronchial tree, the bronchoscope was wedged into a segmental bronchus supplying an area of radiographic abnormalities or into the middle and lingual lobe in case of bilateral diffuse infiltration of the lung. Bronchoalveolar lavage was then performed by segmental instillation and suctioning of 20 ml volumes of physiologic saline solution. The procedure was repeated ten times and the fluids were then pooled.

The BAL specimen was submitted for the following studies:

Gram's stain and aerobic bacterial cultures, both qualitative and quantitative. For quantitative cultures of the lavage specimen, the fluid was diluted with normal saline from 1:10² to 1:10⁴ times. It was then inoculated onto culture media viz. blood agar, MacConkey's agar and chocolate blood agar. Thioglycollate broth was also inoculated if the results of culture plates were negative. A colony count >10⁴cfu/ml was considered significant³⁹. Z-N stain for AFB and BACTEC 460 method for Mycobacterial culture. Direct examination for fungal elements using relevant stains and fungal culture and GMS stain to identify *Pneumocystitis carinii*

Treatment

All patients were treated with empirical antibiotics regimen according to the presenting clinical features. The treatment was modified as warranted either by the need of the patient or depending on the results of investigations performed as part of the study. Patients not responding to treatment were treated with empirical Anti-tuberculosis and/or Anti-fungal drugs.

Response to therapy

The response to therapy was monitored on the basis of clinical improvement and radiological resolution.

The data collected were subjected to basic statistical analysis and appropriate interpretations were drawn.

RESULTS

During the 2 year period, from October 2007 to October 2009, 29 renal transplant patients reported with respiratory symptoms were admitted for inpatient care. Of the 29 patients, 27 reported once, 1 reported twice and another thrice. A total of 32 episodes of respiratory infection were studied. 23 patients were male and 6 were females.

The age range was 18 years to 53 years of age and the mean age of the patients was 31.8 years

The age and sex distribution is given in the following table.

Table 3 - Age and Sex Distribution

	Age Group		Total
	<30years	>30 years	
Male	11	12	23
Female	2	4	6
Total	13	16	29

29 patients in the age range of 18 to 53 were divided into two groups. One was < 30 years and the other was > 30 years.

Table 4 - Source of Donor kidney

		Age Group		Total
		<30years	>30 years	
Live	Male	10	11	21
	Female	1	3	4
Cadaver	Male	1	1	2
	Female	1	1	2
Total		13	16	29

25 (86.2%) patients out of 29 had received the organ from a live related donor and 4 (13.8%) had received from cadavers.

Further analysis was done for 32 episodes of respiratory illness among 29 renal patients.

Table 5 - Time of Respiratory Infection Post Transplant

Period	N = 32(%)
Less than 1 month	2 (6.3)
1 month to 6 months	9 (28.1)
6 months to 1 year	5(15.6)
1 to 2 years	4(12.5)
More than 2 years	12(37.5)

While analyzing the time of infection since transplantation, it was found that 2 (6.3%) patients presented less than a month from transplant surgery, 9 (28.1%) patients from 1 month to 6 months, 5 (15.6%) patients from 6 months to 1 year, 4 (12.5%) patients from 1 to 2 years and 12 (37.5%) patients more than 2 years since transplant surgery. Out of this the shortest period was 4th post operative day and the longest being 9 years after transplant surgery.

Table 6 - Risk Factors

Condition		N=29(%)
H/O Acute rejection		11(37.93)
PTDM		4(13.8)
H/O CMV infection		3(10.34)
H/O Hepatitis	B	1(3.4)
	C	2(6.9)
Pre transplant DM		1(3.4)
No identifiable risk factors		7(24.13)
TOTAL		29(100)

On analyzing risk factors for developing respiratory infections, history of acute graft rejection was found in 11 patients (37.93%) and had received anti rejection therapy with pulse Methyl prednisolone. 4 patients (13.8%) had Post transplant diabetes mellitus and one (3.4%) had diabetes mellitus prior to transplant. Prior history of cytomegalo virus infection was present in 3 patients (10.34%). 3 patients (10.3 %) were suffering from hepatitis, 2 from Hepatitis C and 1 from Hepatitis B infection. There was no identifiable risk factors in 7 patients(24.13%).

Table 7- Immunosuppressive Therapy Frequency

Immunosuppressive Therapy	N = 29 (%)
----------------------------------	-------------------

CsA+S+A	22 (75.86%)
CsA+S	1 (3.45%)
A+S	1(3.45%)
Tacrolimus+MMF+S	4 (13.79%)
CsA+MMF+S	1(3.45%)
TOTAL	29 (100%)

CsA – Cyclosporin A, S- prednisolone,
A- Azathioprine, MMF- Mycophenolate Mofetil

On analyzing the immunosuppressive therapies administered to transplant recipients, It was found that 22 patients (75.86%) were under triple immunosuppressive therapy which included Cyclosporin A, Prednisolone and Azathioprine. All 4 patients (13.79%) who received their donor organ from cadaver were given Tacrolimus, MMF and Prednisolone.

Table 8 - Chest Symptomatology

Symptoms	N=32(%)
Fever	27(84.3)
Cough Expectoration	22(68.75)
Loss of Appetite	11(34.3)
Breathlessness	11(34.3)
Weight loss	6(18.75)
Chest pain	5(15.6)
Hemoptysis	2(6.2)

Fever was the chief presenting complaint in 27 episodes (84.3%). Cough with expectoration was present in 22 (68.75%) episodes. shortness of breath was present in 11 episodes (34.3%). Loss of appetite was present in 11 episodes (34.3%) and of which 6 episodes (18.75%) presented with significant weight loss. 5 episodes (15.6%) presented with chest pain and 2 episodes (6.2%) had hemoptysis.

The mean duration of symptoms before admission during the study was 6.12 days. One patient had developed symptoms on the 4th post operative day of the transplant while 1 patient reported after a month of symptoms to the hospital.

Table 9 - Radiological Manifestations at presentation

Radiological Features	N-32(%)
Air space opacities/ Consolidation	23(71.87)
Pleural effusion	4(12.4)
Nodules	1(3.1)
Fibrocavity	1(3.1)
Miliary	1(3.1)
Normal	2(6.2)
TOTAL	32(100)

On analyzing radiological manifestations of pulmonary infection, 23 (71.87%) patients had presented as air space opacities / consolidation, 4 (12.4%) patients had presented as pleural effusion, 1 patient (3.1%) each of miliary nodules and Fibro cavity and was normal in 2 (6.2%) patients.

Microbiology

Sputum

Sputum was available for test in only 25 patients. Sputum specimens in 17 episode were positive for gram negative bacilli, in 8 with gram positive cocci, 1 with gram positive bacilli and in one episode both gram positive bacilli and gram positive cocci. KOH mount positive for fungal elements in one episode.

Sputum ziehl-neelson staining for Acid fast bacilli was positive in 2 patients (6.25 %)

Table 10 - Sputum Bacterial Culture

	N=32(%)
Pseudomonas	4(18.18)
Klebsiella	4(18.18)
Pseudomonas+Klebsiella	1(3.12)
Staph.aureus	1(3.12)
Mycobacterium tuberculosis	2(6.25)
Candida	1(3.12)
No Sputum available	7 (21.87)
No identifiable Organism	12(37.5)
TOTAL	32(100)

Sputum for bacterial culture grew pseudomonas and klebsiella species in 4 patients (18.18%) each and one patient (3.12%) grew both pseudomonas and klebsiella. Staphylococcus aureus species was isolated from another patient. Sputum fungal culture grew candida species in one patient. Sputum bacterial culture showed no growth in 12 patients (37.5%).

BAL (Bronchoalveolar Lavage)

Broncho alveolar lavage was done in 30 episodes excluding 2 patients who were sputum smear positive for AFB.

The diagnostic yield of BAL is given in the following table.

Table 11- Diagnostic Yield of BAL Microbial Analysis

Diagnostic yield	N=32(%)
Single organism	22(68.75%)
Multiple organism	5(15.625)
No growth	3 (9.375)
BAL not done	2(6.25)
TOTAL	32(100)

The Diagnostic yield of BAL, 22 episodes with single organism infection and 5 episodes with multiple organisms infections were made out. In 3 episodes no organisms could be isolated.

BAL specimens in 19 episodes were positive for gram negative bacilli, in 8 with gram positive cocci, 2 with gram positive bacilli and another 2 episodes both gram positive bacilli and gram positive cocci. KOH mount positive for fungal elements in 3 episodes. BAL Ziehl-neelson staining for Acid fast bacilli was positive in 7 patients.

Table 12 - Spectrum of Micro organisms isolated from BAL fluid

Organism		N=30			%
		Single Organism N =22	Multiple Organism N=5	No organism	
Bacteria	Pseudomonas	8			26.6%
	Klebsiella	2			6.6%
	Pseudomonas+ Klebsiella		2		6.6%
	Staph.aureus	1			3.33%
	Acinetobacter +Klebsiella		1		3.33%
	Nocardia	1			3.33%
	CONS	1			3.33%
Mycobacteria		6			20%
	+ Flavobacterium Sps + Pseudomonas		1		3.33%
Fungus	P.carinii	1			3.33%
	Candida	2			6.6%
	Aspergillus + E.coli		1		3.33%
No organisms isolated				3	10%
TOTAL		22	5	3	100%

Bacterial Culture

In BAL bacterial culture, 16 episodes showed evidence of bacterial infection and a total of 22 bacterial species were isolated. In 5 episodes multiple bacterial organisms were isolated and in rest single organism was isolated. Of the multiple infections, Pseudomonas coinfection with Klebsiella were present in 2 episodes, Acinetobacter coinfection with Klebsiella were present in one episode. Mycobacterial infection with Flavobacterium species and Pseudomonas in one episode and Aspergillus flavus infection with E.coli in one episode.

In the rest, single organism was present in 13 episodes. Of it most common was pseudomonas species grown in 8 (26.6%) episodes, Klebsiella in 2 episodes and Staphylococcus.aureus, Nocardia, Coagulase negative staphylococcus one each. BAL bacterial culture in 12 episodes showed no growth.

BAL Ziehl - Nielson Stain

BAL Ziehl-nielson staining for acid fast bacilli was positive in total of 7 patients. Isolated Mycobacterial infection in 6 patients and in one patient it was associated with Flavobacterium and Pseudomonas organisms. These were confirmed with BAL BACTEC 460 method.

Grading of BAL AFB was as follows, 1+ in 5 patients and one each of 2+ and 3+.

BAL Fungal Culture

IN BAL fungal culture, Candida species were isolated in 2 patients and Aspergillus in one patient. BAL GMS stain for Pneumocystitis Jeruvici was positive in one patient.

No organisms were isolated in 3 episodes.

Table 13 - Spectrum of Microbes in Relation to Duration Post Transplant Surgery

Period	Bacterial									Myco bacterium	Fungal			No Organism Isolated
	Ps	Kl	Ps+ Kl	S.a	Fl	E	N	C	Kl+A		Can dida	Asper gillus	PCP	
Less than 1 month		1												1
1 month to 6 months	3	1	1		1				1	2	1		1	
6 months to 1 year	1	0	1			1				1		1		
1 year – 2 year				1						1	1			1
More than 2 year	4						1	1		5				1

Ps - Pseudomonas-, Kl - Klebsiella, Ps + Kl - Pseudomonas+Klebsiella, S.a Staph.aureus, Fl - Flavobacterium, E - E.coli, N - Nocardia, C - Coagulase negative staphylococcus aureus, Kl+ A - Klebsiella+Acinetobacter

On analysis of spectrum of respiratory infections in relation to duration post transplant following observations were made.

In period less than a month, two (6.25%) episodes of respiratory infections were

observed in this study and one was a bacterial infection with klebsiella species and no organism could be isolated in the other.

9 episodes (28.125%) in between 1 month and 6 months of transplant surgery. Of these 3 episodes were with multiple organisms. 7 were bacterial infections, 2 were mycobacterial infections and 1 fungal infection. The only episode of PCP infection of this study also presented during this period.

5 (15.625%) episodes presented during the period 6 months to 1 year. Of these 2 were with multiple organisms. It constituted of 3 bacterial, 1 mycobacterial and 1 *Aspergillus flavus* infection. This fungal infection was a multiple infection with *E.coli*.

4 (12.5%) episodes presented between 1 year and 2 years of transplant surgery. 1 bacterial, 1 mycobacterial and 1 candida infection. No organism could be isolated in one episode.

12 (37.5%) episodes after 1 year of transplant surgery. Of these 6 were bacterial and 5 were mycobacterial. In one episode no organism could be isolated. The only episode of nocardial infection in this study presented in 14th month post transplant surgery and this patient was suffering from hepatitis, a known risk factor for nocardial infection. All the episodes of multiple infections (5 episodes) present within 1 year of duration since transplant surgery and of the total 32 episodes, No organism could be isolated in 3 (9.375%) episodes.

Table 14 - Spectrum of Respiratory infections in Relation to Radiographic Findings

	Air space opacities /Consoli dation	Pleural effusion	Nodule s	Fibro cavity	Miliar y	Norma l	Total
Bacterial Infection	12	3	1				16
Mycobacterium Tuberculosis	6			1	1	1	9
Aspergillus	1						1
Candida	2						2
PCP	1						1
No definite diagnosis	1	1				1	3
TOTAL	23	4	1	1	1	2	32

On analysis of spectrum of microbes in relation to radiographic findings, following observations were made. Of the 16 episodes of bacterial infections, 12(75%) episodes presented with radiologic feature of air space opacities/consolidation, 3 with pleural effusion and 1 with nodular opacity. Nocardial infection presented as nodular opacity.

Mycobacterial infection presented with following radiological findings. 6 episodes presented with features of air space opacity and one each with features of fibro cavity, miliary pattern.

Fungal infections and Pneumocystitis pneumonia presented with features of air space opacity.

Table 15 - Spectrum of Respiratory Infections in Relation to Immunosuppressive Therapy

Immunosuppressive Therapy	Bacterial									Myco bacterium	Fungal		
	P s	Kl	Ps+Kl	S.a	F l	E	N	C	Kl+A		Can dida	Asper gillus	PCP
CsA+S+A	6		2	1	1	1	1	1		8	1	1	1
CsA+S	1												
A+S										1			
Tacrolimus+MMF+S	1	2									1		
CsA+MMF+S									1				

Ps - Pseudomonas-, Kl - Klebsiella, Ps + Kl - Pseudomonas+Klebsiella -3, S.a -Staph.aureus, Fl - Flavobacterium, E - E.coli, N - Nocardia, C - Coagulase negative staphylococcus aureus, Kl+ A - Klebsiella+Acinetobacter CsA – Cyclosporin A, S- prednisolone, A- Azathioprine, MMF- Mycophenolate Mofetil

On analysis of respiratory infection in relation to immunosuppressive therapy, following observations were made. Respiratory infections either bacterial, mycobacterial or fungal were common in patients with triple drugs immunosuppressive therapy with Cyclosporin-A, Prednisolone, and azathioprine. Out of the 9 Mycobacterial infections, 8 were present in patients on cyclosporine A containing immunosuppressive therapy.

Table 16 - Drug Sensitivity Pattern in Bacterial culture

Drugs	N=18 (%)
Ciprofloxacin	14(77.77)
Amikacin	12(66.66)
Cefaperazone sulbactum	9(50)
Ofloxacin	6(33.33)
Gentamycin	6(33.33)
Piperazaline-Tazobactum	3(16.66)
Cefatoxime	3(16.66)

On analysis of drug sensitivity pattern of bacterial culture, following observations were made. Ciprofloxacin was sensitive in 14 out of 18 episodes (77.77%) of bacterial infections. In 12 out of 18 episodes (66.66%) Amikacin was sensitive and Cefaperazone sulbactum sensitive in 9 episodes (50%) of bacterial infections.

DISCUSSION

Bacteria, known to be the most common cause of pneumonia in the immunocompromised individual³, have been found to be the major cause of post transplant pulmonary infections in other studies too. In other Indian studies the incidence of bacteria has been found to range from 25% to 33.3%. In our study, bacteria, account for 62.8% of all the organisms diagnosed (22 out of 35 organisms). The exact incidence of bacterial pneumonia among transplant recipients is difficult to assess because broad spectrum antibiotics are empirically started early upon admission. Munda et al⁹ found that 69.5% of the causative organisms in 46 episodes of post transplant pulmonary infection were bacteria. This high incidence has been attributed by the authors to their use of transtracheal percutaneous puncture for the isolation of the organism. In the study by Webb¹² et al, 52 organisms were isolated from the 44 episodes. They found 68.8% of the organisms to be bacteria. In the study by Modi et al in AIIMS, found bacterial infection to be 27.7% in 18 episodes of respiratory infections in post renal transplant patients. Jha V et al quoted a bacterial infection incidence as 33.3% and Vikram kalra et al found the bacterial infections to be 45.4%.

In India, tuberculosis being an endemic disease poses a formidable challenge to the clinician dealing with transplant recipients despite the advances in diagnostic facilities and chemotherapy²⁹. This is expected since the prevalence of tuberculosis in general population in India is higher. Lung tuberculosis has been reported to occur with

10-25 times higher frequency in immunosuppressed patients⁶. Recent Indian data^{34,35} shows a higher incidence of pulmonary tuberculosis in this group of patients, ranging from 30-50%. Modi et al³⁵ reported Tuberculosis incidence of 50%. Jha V et al³⁴ reported an incidence of 30.7%. Vikram kalra et al³¹, found the incidence of tuberculosis in post renal transplant patients to be 36.3%. As quoted in the previous study, this is probably because of the use of bronchoscopy in the isolation of the organism in the recent studies. Our study reported an incidence of 28.12% of pulmonary tuberculosis in the renal transplant recipients. The time range for development of tuberculosis infection was from 2.7 months to 8.7 years, with a mean of 3.38 years. 7 out of the 9 tuberculosis patients developed the illness in less than 6 years period from transplant surgery. All these 7 patients were on triple immunosuppressive drugs (Cyclosporine, Azathioprine and steroids). Of the 2 developing tuberculosis beyond 6 years duration, 1 was on non cyclosporine containing immunosuppressive therapy (Azathioprine and steroids) and the other on triple immunosuppressive drugs. This in accordance with the study by John et al, CMC vellore determining a timetable for post transplant infections in the tropics³⁶ concluded that most patients on CsA who are likely to develop post transplant tuberculosis will have developed the disease by six years.

P. jirovecii is an opportunistic pathogen especially observed in patients with impaired cellular immunity³⁷. In our study, there was one episode (2.85%) of PCP. It presented in 5th month, Post transplant surgery. In recent studies in India, the incidence of PCP among this group of patients was from 6% to 27%

Multiple organism infections were noted in 5 episodes (14.28%). 4 of this had 2 organisms and one case had 3 organisms as etiology. Tuberculosis with *Pseudomonas* and *flavobacterium* infection & *Aspergilosis* with *E.coli* was noted one each and the other 3 were mixed bacterial infections. 2 cases with *pseudomonas* & *Klebsiella* and one case with *Acinetobacter* and *klebsiella*. More than one organism being the cause of infection has been seen in other studies too. Jha R et al³⁰ found 4 cases to have a mixed aetiology of the 27 cases they studied. In the study by Jha V et al³⁴, more than one organisms were implicated in 5 episodes out of 39. Out of these 5, the second organism was diagnosed only on autopsy in 3 cases and on BAL in the other 2. Heurlin et al¹⁵ could isolate multiple organisms in 6 out of 34 cases. In 4 of these 6 instances, the isolation was on bronchoscopy. Munda et al⁹ found mixed infections in 11 cases of the 46 they studied. In their study only 4 patients underwent bronchoscopy, more than one organism being isolated in 1 patient out of these 4. In the study by, Vikram kalra et al³¹, Out of the 44 episodes of pulmonary infection evaluated, multiple etiologies were found in 15 (34.1%) episodes. based on BAL. Thus, it appears that the use of BAL may be an important factor also in isolation of more than one organism and establishing a multiple aetiology.

Herpes, Influenza, parainfluenza and adenovirus are the group of viruses which causes respiratory tract infections in renal transplant recipients. Among these CMV is the most frequent pathogen encountered^{18,19}. It frequently occurs 1-4 months after transplantation, when both allograft rejection and intensive immunosuppressive treatment occur. The clinical onset of CMV pneumonia is usually insidious with slowly

progressing, relapsing fever, alternating between afebrile and 40° C along with fatigue. CMV infection was not well recognised among renal transplant recipients in tropical countries because of lack of proper diagnostic facilities^{21, 38}.

Our study did not include investigations related to viral etiology due to lack of facilities to identify and isolate the same in our institution.

CONCLUSION

The present study concluded that:

1. Fever and cough with expectoration were the most common clinical presentation.
2. Bacteria were the most prevalent cause of post transplant pulmonary infection.
3. Pseudomonas and klebsiella were the most common bacterial species causing respiratory infections among renal transplant recipients.
4. Tuberculosis also has a high incidence in renal allograft recipients in our set up.
5. Mixed infection is common among renal transplant recipients and search for the aetiologic agent should not stop at the isolation of one organism especially if the response to therapy against a single aetiologic agent is partial and/or delayed. The presence of more than one organism should be conclusively ruled out.
6. Bronchoalveolar lavage is one of the most important diagnostic aids and has a high diagnostic yield.

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ABBREVIATION

BAL	-	Bronchoalveolar Lavage
GMS Stain	-	Gomori methenamine silver stain
CMV	-	Cytomegalo virus
Z-N stain	-	Ziehl – Nielson stain
AFB	-	Acid Fast Bacilli
CT chest	-	Computerised Tomography chest
CXR	-	Chest X-Ray
SGOT	-	Serum Glutamate Ornithine Transaminase
SGPT	-	Serum Glutamate Pyruvate Transaminase
KOH	-	Potassium Hydroxide
PTDM	-	Post Transplant Diabetes mellitus
CsA	-	Cyclosporin A
MMF	-	Mycophenolate Mofetil

APPENDIX I

QUESTIONNIERE

Name:

Height:

Weight:

BMI:

Date of admission:

Original disease:

Case No.

Age:

Sex:

Occupation:

Date of Transplant Surgery:

Source of organ:

Living Conditions:

City/ Rural

Type of House

Ventilation condition

Sanitation

Location of kitchen

Source of Water:

Toilet habits:

Fuel for cooking:

H/O present illness

Symptoms

Cough/expectoration

Fever

Breathlessness

Chest pain

Hemoptysis

Duration

H/O past illness

H/O previous infections:

H/O graft rejection (creatinine >1.5mg %):

H/O Anti-rejection therapy:

Diabetes Mellitus

CMV, TB, HCV, HBV

DRUGS HISTORY:

Current medication:

Recent medication changes:

Immunosuppressive Therapy:

Compliance of Therapy:

RESULTS

FOB Report:

Blood Report

Sputum Report

BAL Report

Radiology

